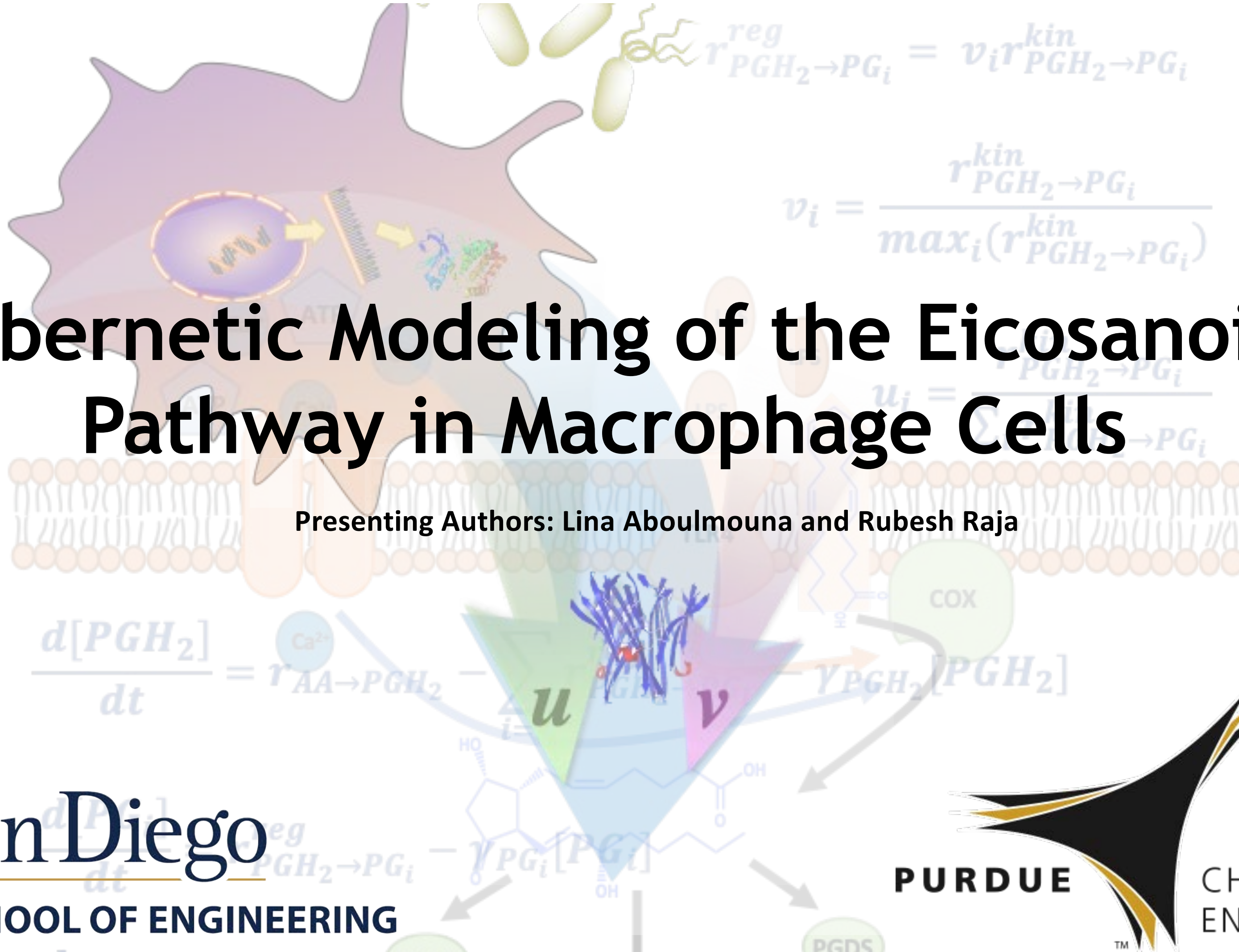


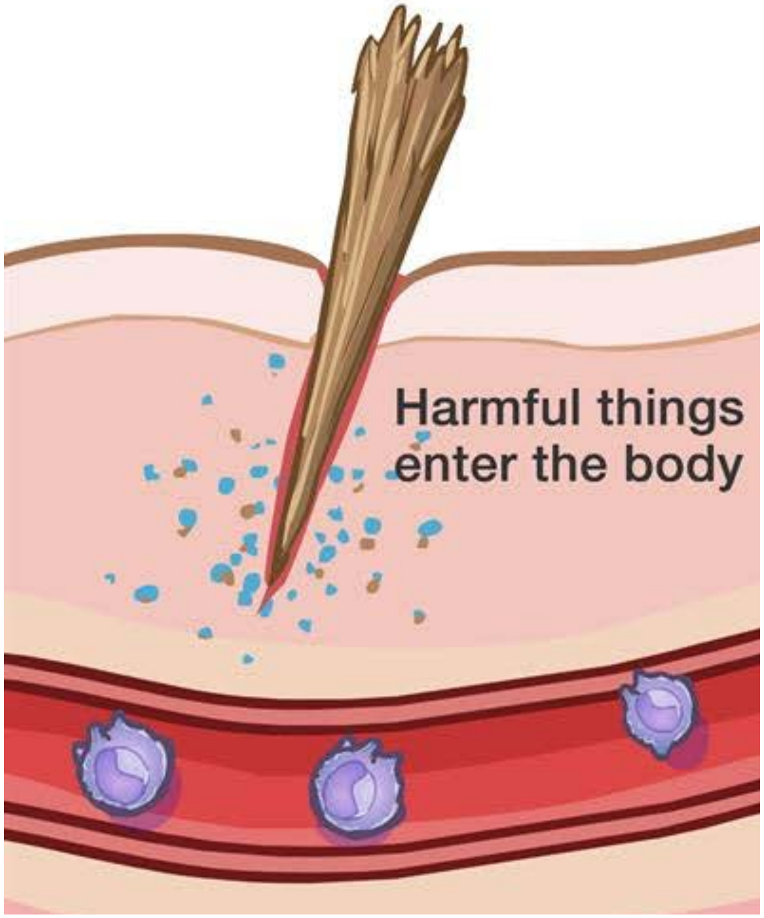
Cybernetic Modeling of the Eicosanoid Pathway in Macrophage Cells

Presenting Authors: Lina Aboulmouna and Rubesh Raja

UC San Diego
JACOBS SCHOOL OF ENGINEERING

PURDUE CHEMICAL ENGINEERING

Inflammation: The body's 2nd line of defense



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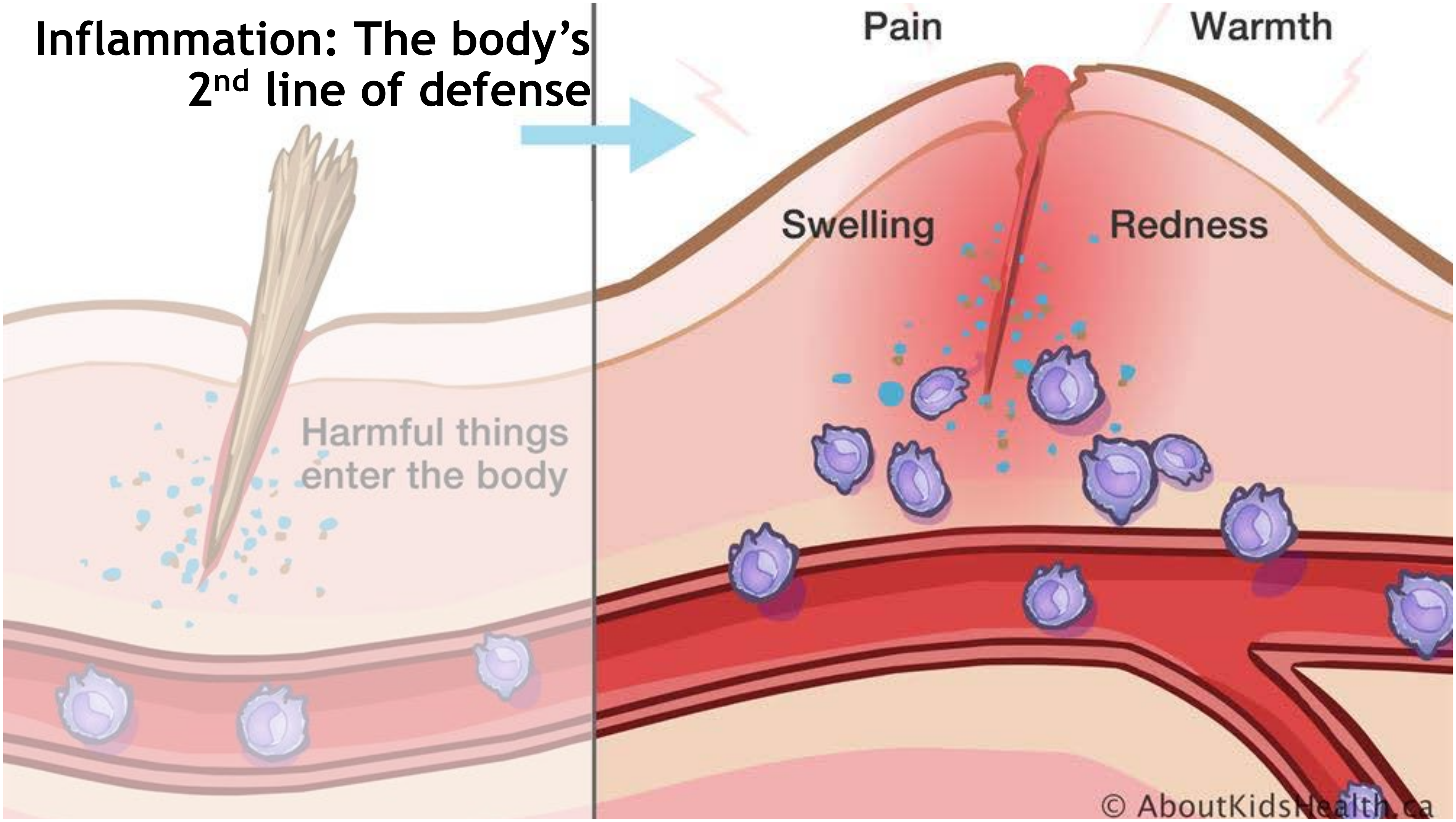

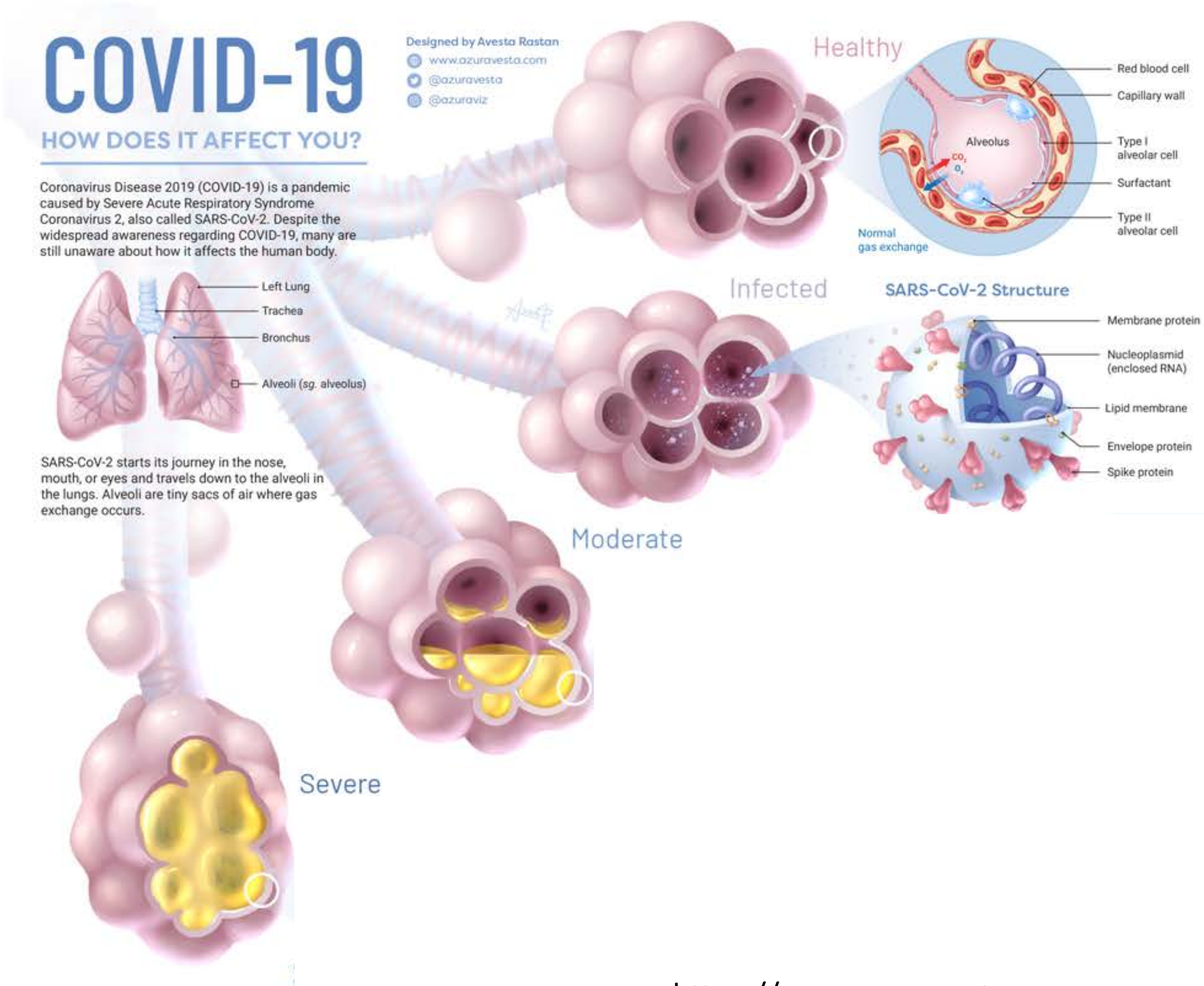

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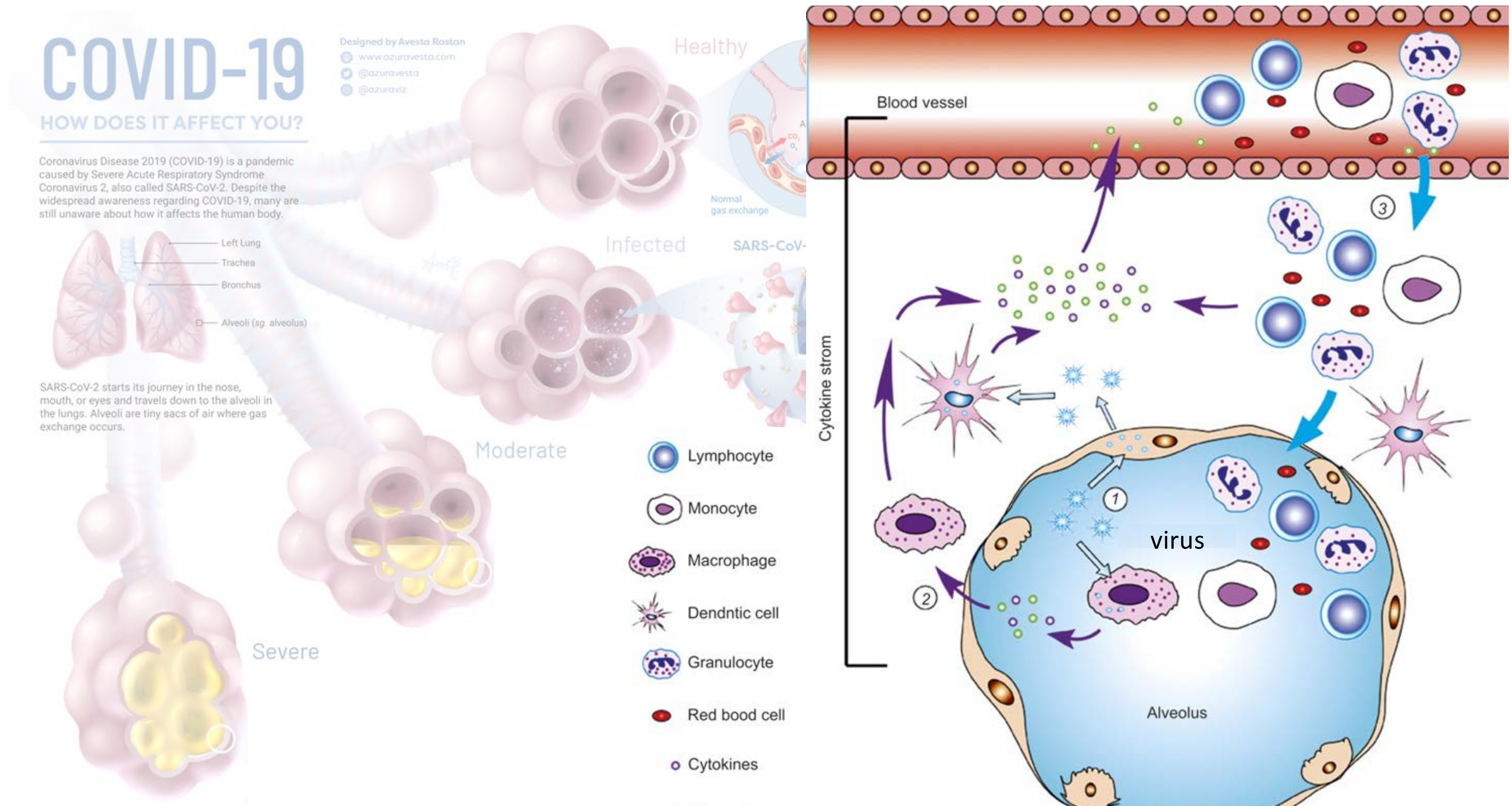
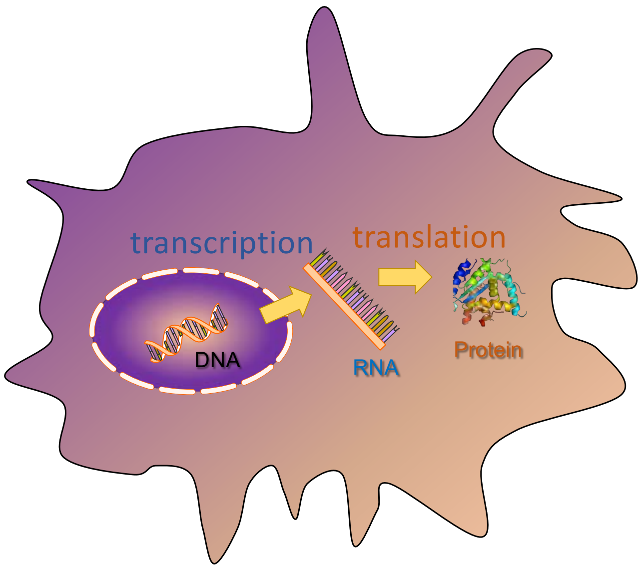


Liu, Q., Zhou, Y. & Yang, Z. The cytokine storm of severe influenza and development of immunomodulatory therapy. *Cell Mol Immunol* **13,** 3–10 (2016).

Mimicking the physiological response of Infection



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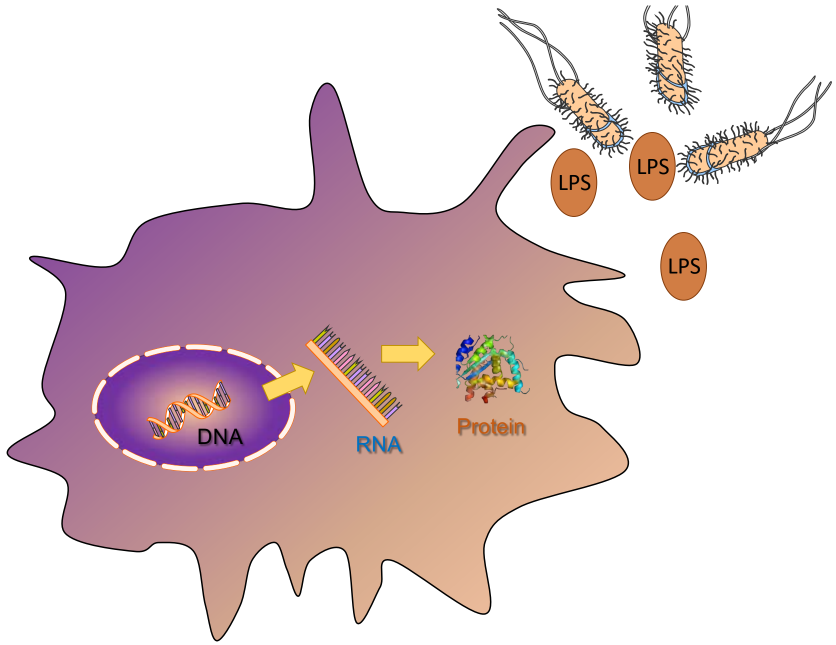

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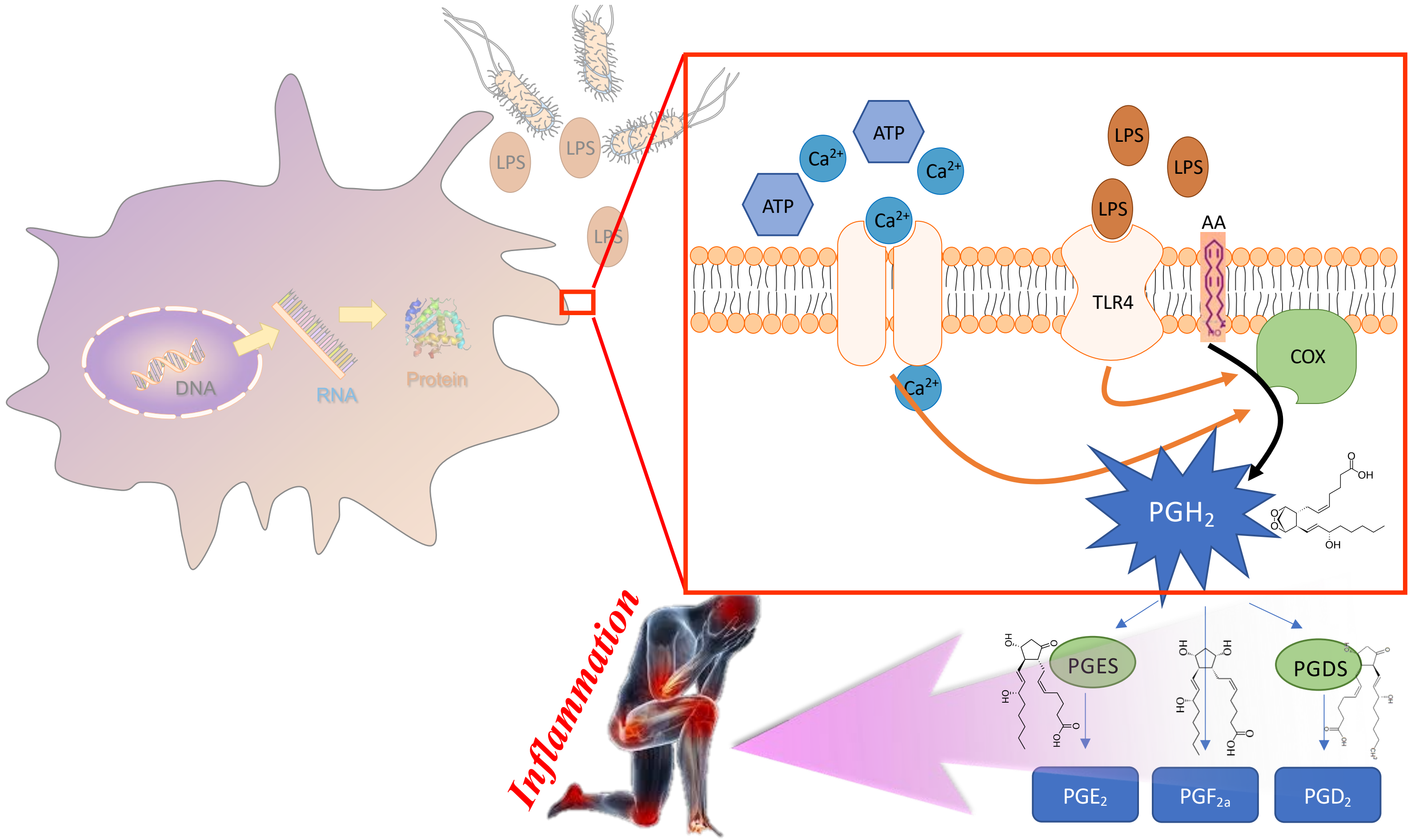

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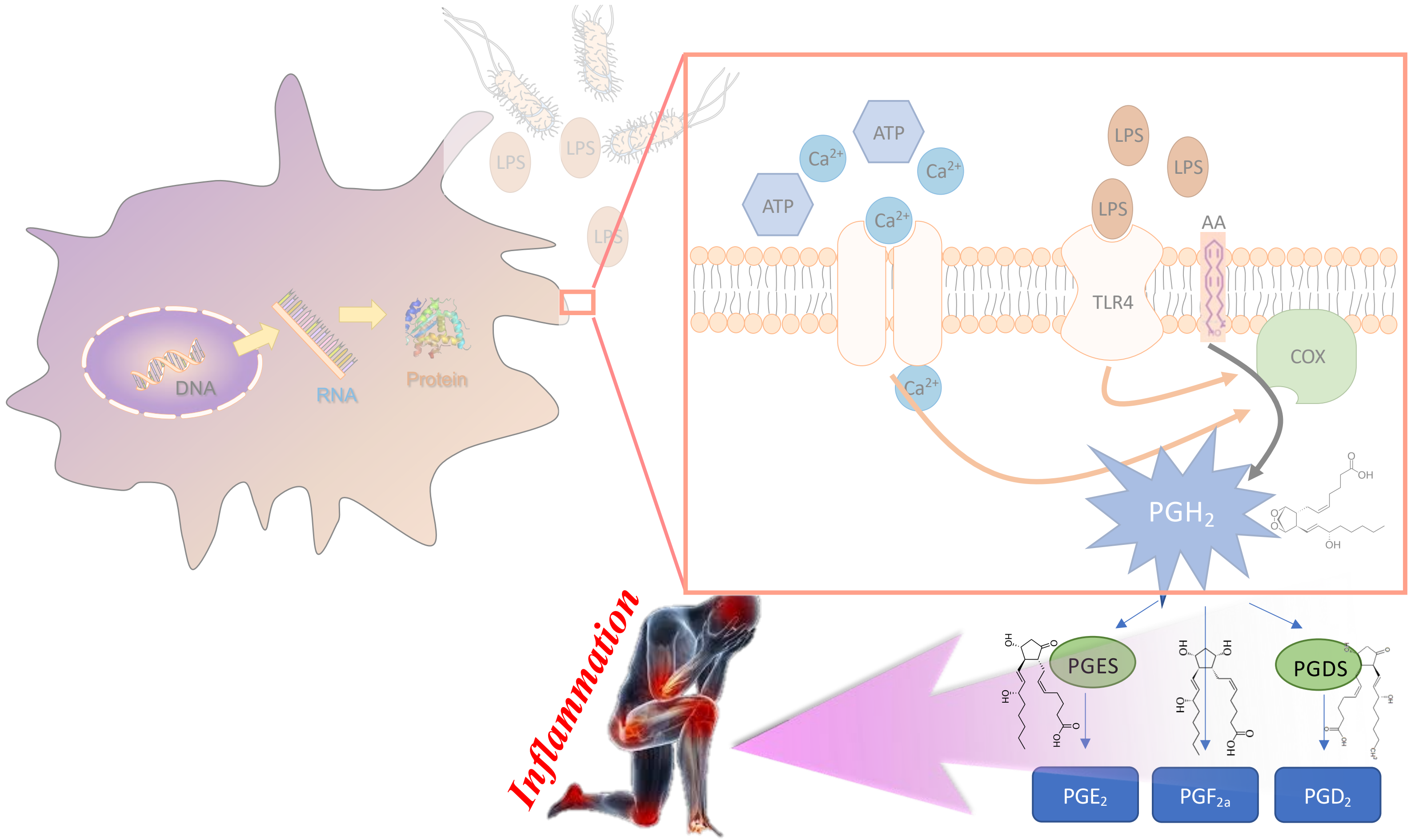

Standard Mathematical Modeling for Biological Networks

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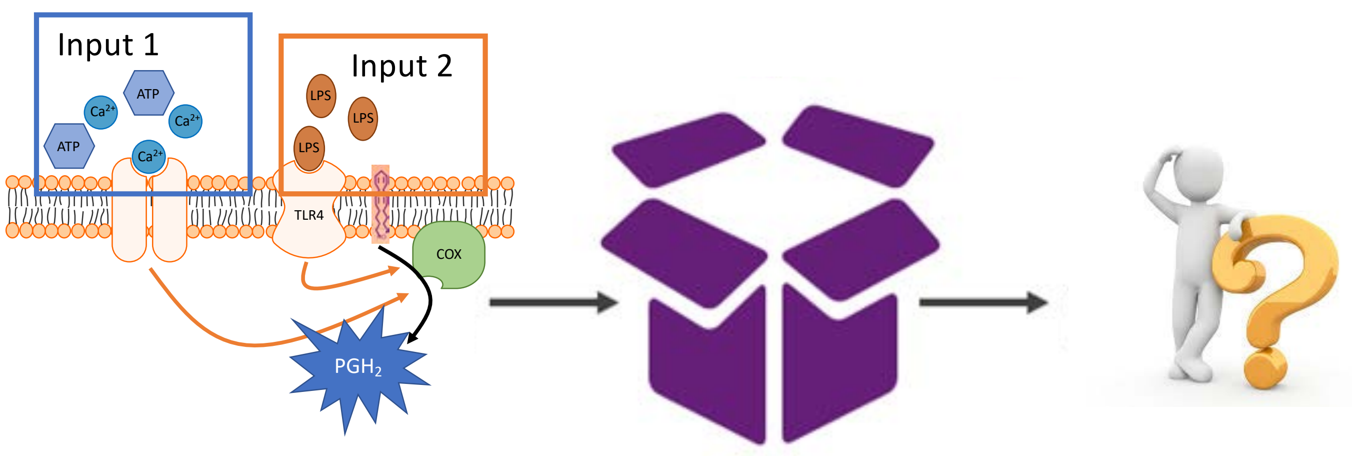
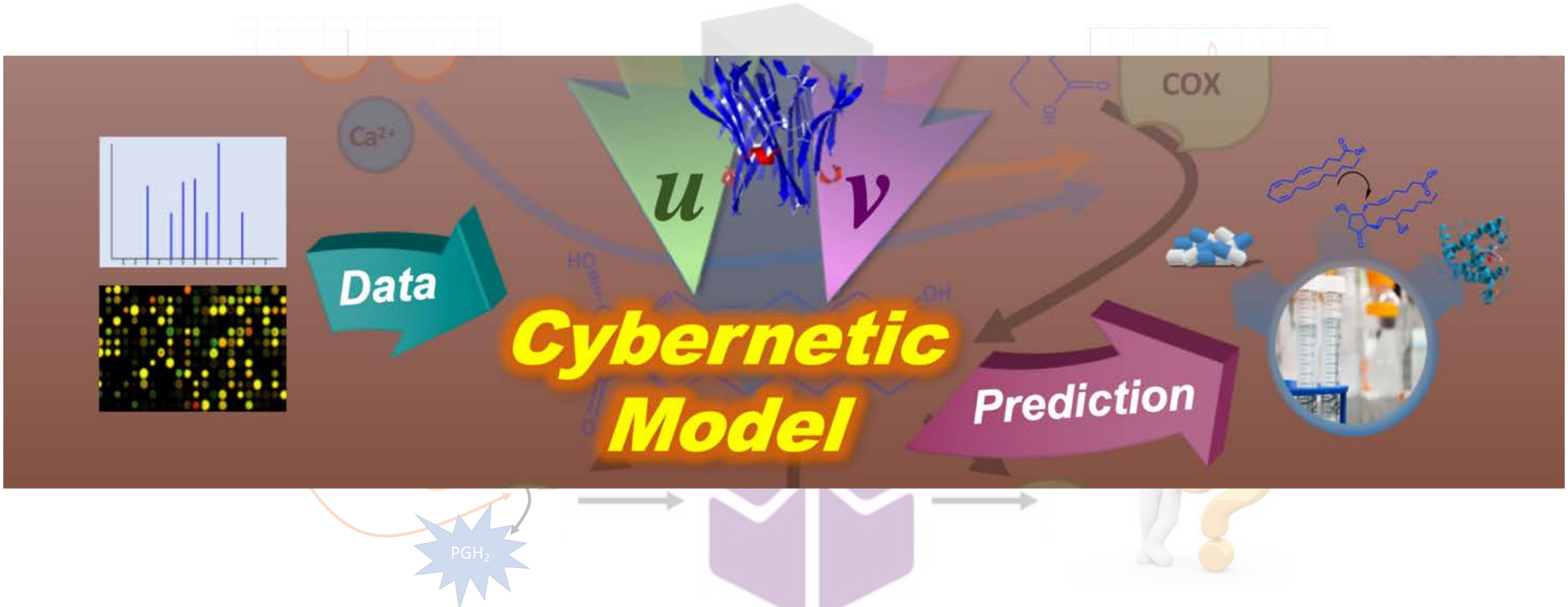
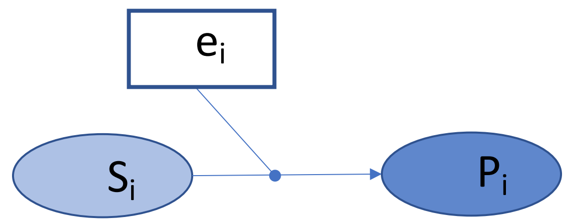


Alternate modeling framework: Cybernetic model



Reaction Kinetics

Reaction Framework:

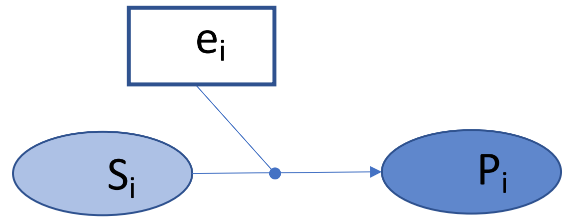


$$\frac{dP_i}{dt} = k_i e_i S_i - g_i P_i$$

$$\frac{de_i}{dt} = k_{e,i} S_i - \beta_{e,i} e_i$$

Introducing cybernetic control variables

Reaction Framework:



$$\frac{dP_i}{dt} = v_i k_i e_i S_i - g_i P_i$$

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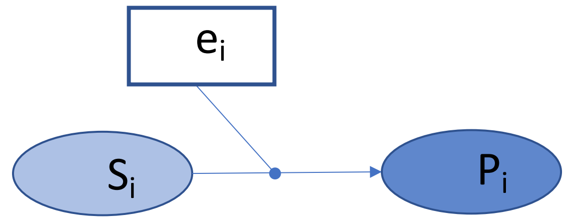

Activity Control

$$\frac{dP_i}{dt} = \boxed{v_i} k_i e_i S_i - g_i P_i$$

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Introducing cybernetic control variables

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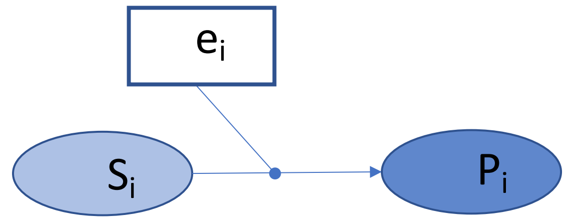

$$\frac{dP_i}{dt} = v_i k_i e_i S_i - g_i P_i$$

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Synthesis Control

Defining cybernetic control variables

Goal: Survival

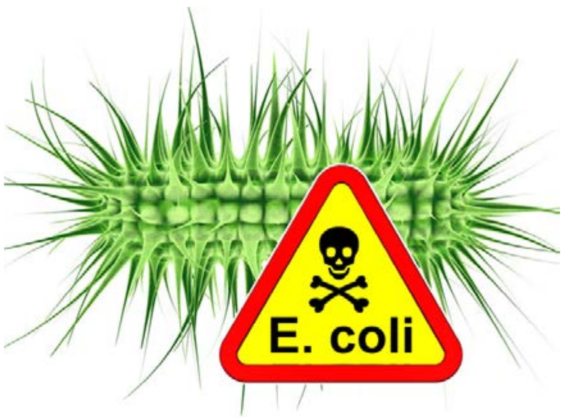
Specific goal: Maximize biomass production rate within available resources

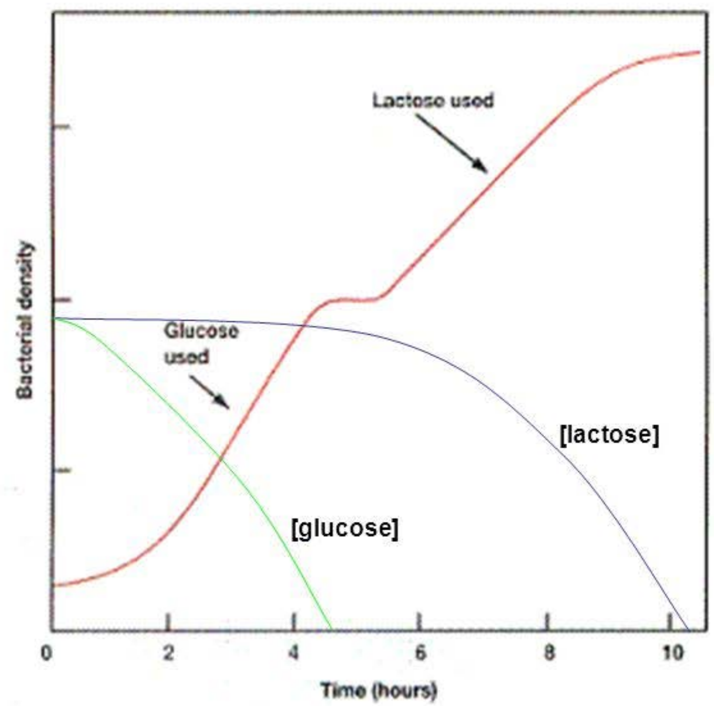
Return on investment: $\rho_i = r_{S_\mathrm{i} \to P_i}^{unregulated} = k_i e_i S_i$

$$v_i = \frac{\rho_i}{\max_j \rho_j}$$

$$u_i = \frac{\rho_i}{\sum_j \rho_j}$$

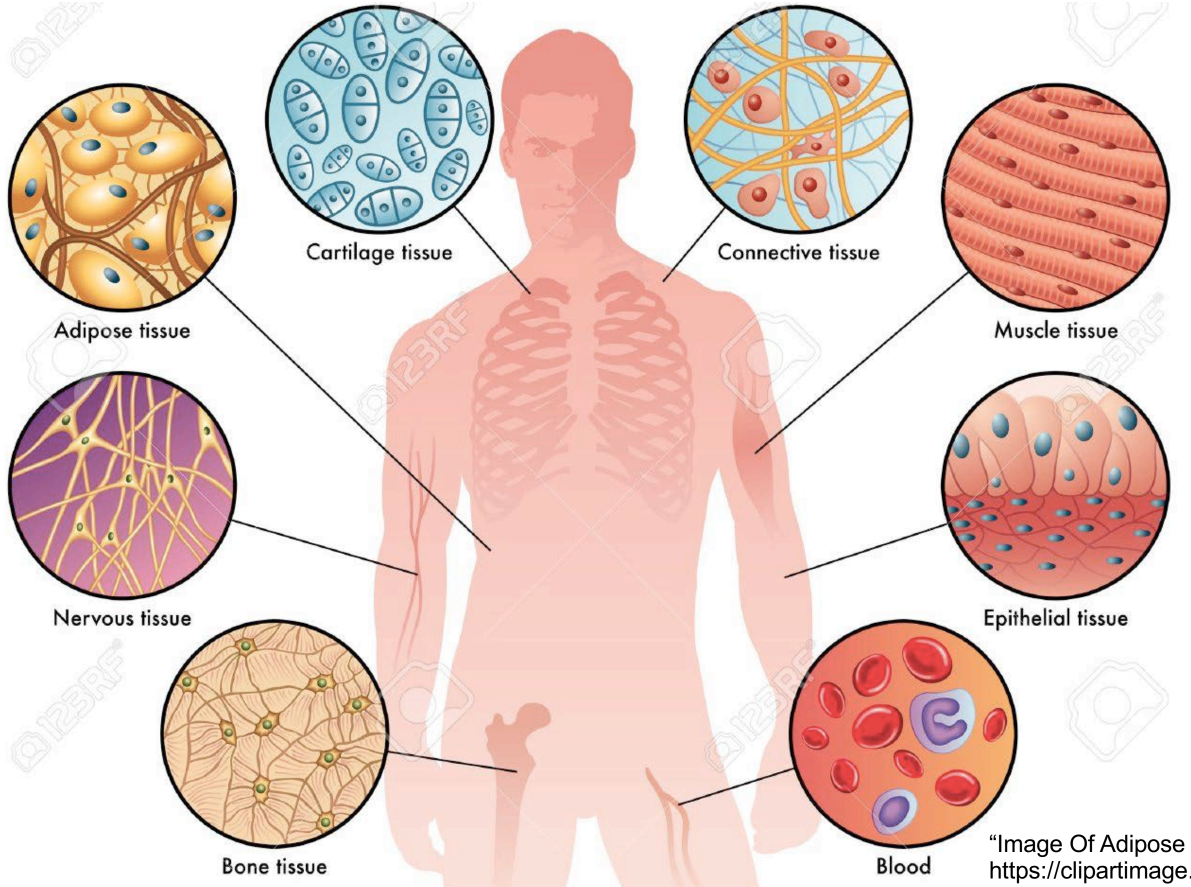
Diauxic growth of E. coli





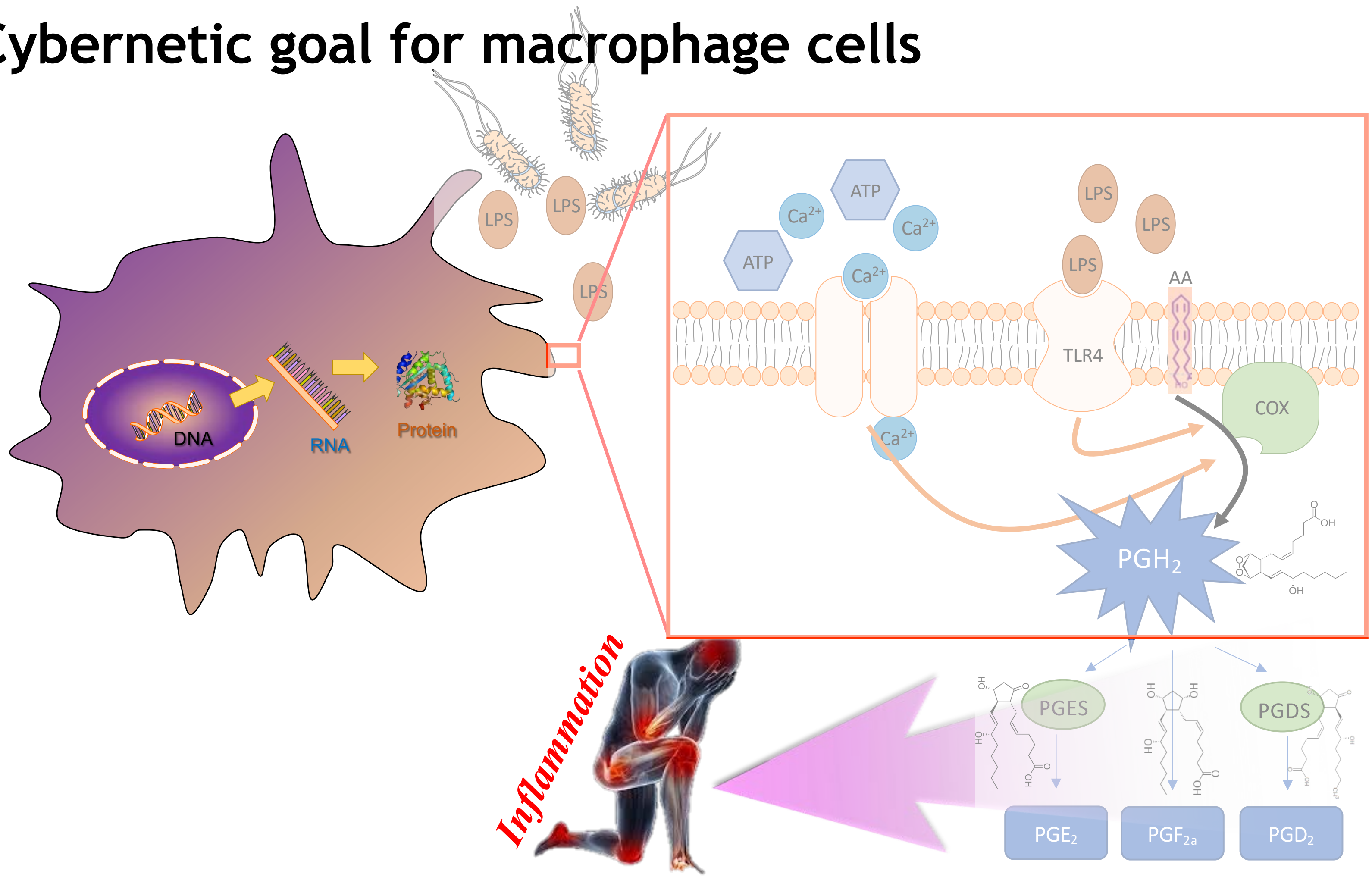
Kompala, D.S., et al., *Investigation of bacterial growth on mixed substrates: experimental evaluation of cybernetic models.* Biotechnol Bioeng, 1986. **28**(7): p. 1044-55.

Multicellular Systems

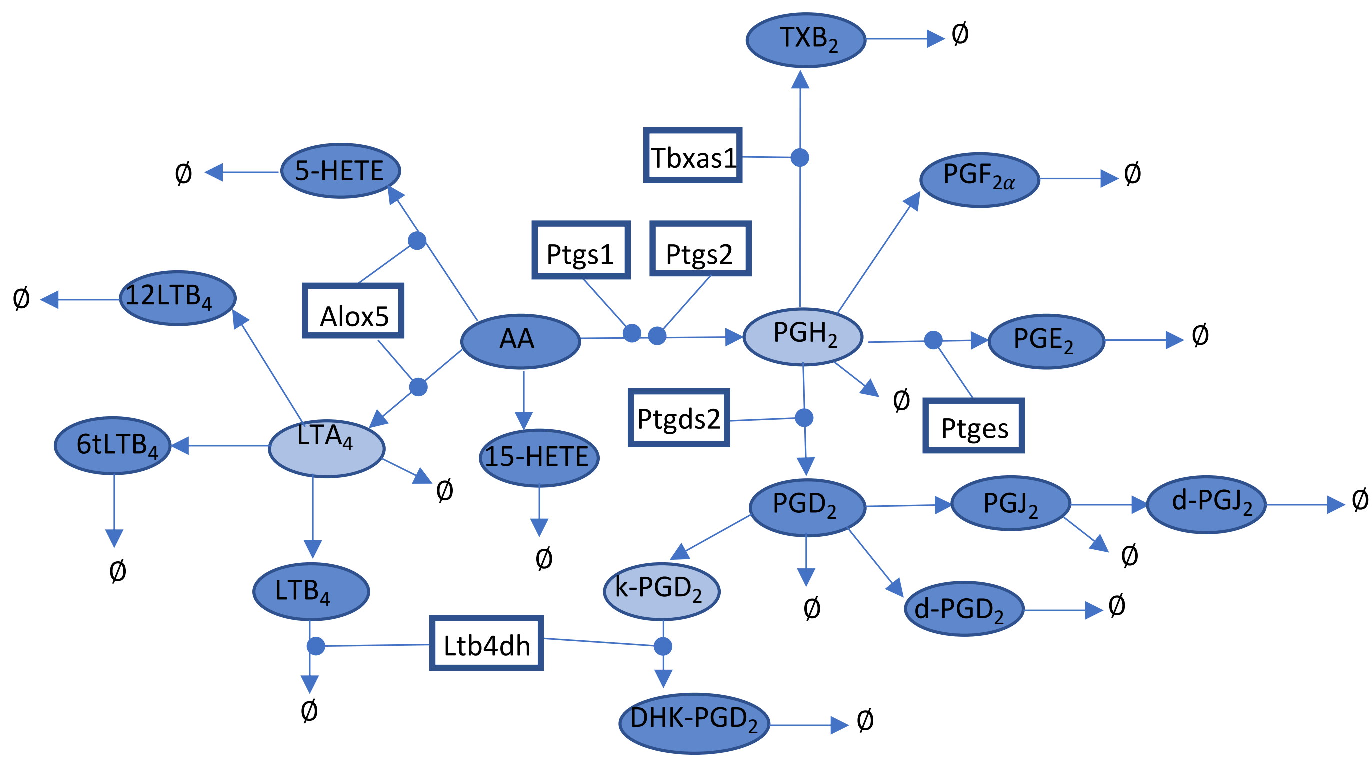


"Image Of Adipose Tissue In A Human Body Clipart"
https://clipartimage.com/images/clipart-367516.html

Cybernetic goal for macrophage cells

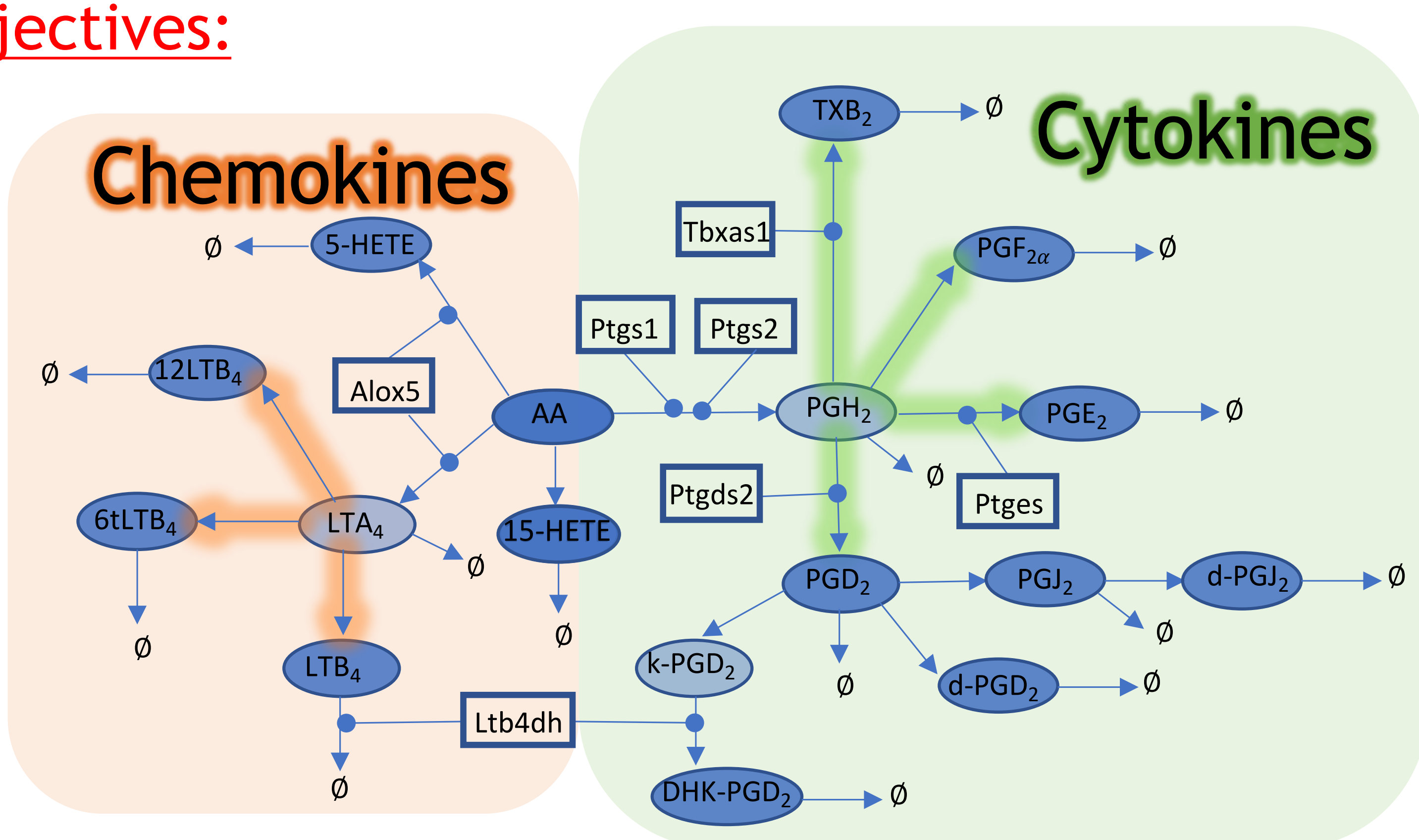


Eicosanoid Metabolism

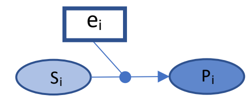


Cybernetic Model of Eicosanoid Metabolism

2 objectives:

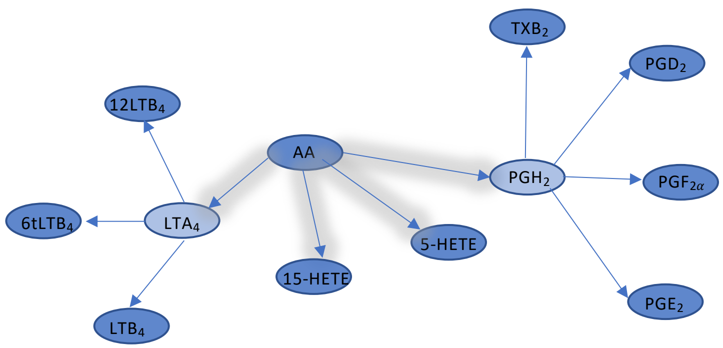


Part1: Kinetic model

Reaction Framework: 

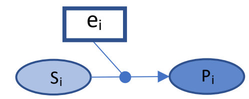
$$\frac{dP_i}{dt} = k_i e_i S_i - g_i P_i - (downstream\ fluxes)$$

$$\frac{de_i}{dt} = k_{e,i} S_i - \beta e_i$$



Part2: Cybernetic Regulation with Cytokines

Reaction Framework:



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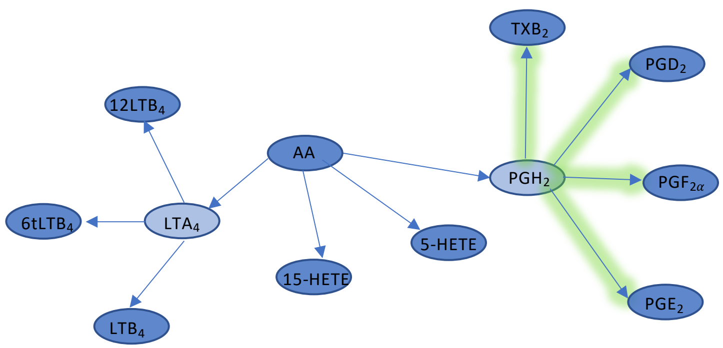
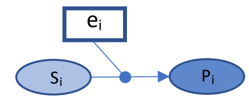


Part3: Cybernetic Regulation with Chemokines

Reaction Framework:



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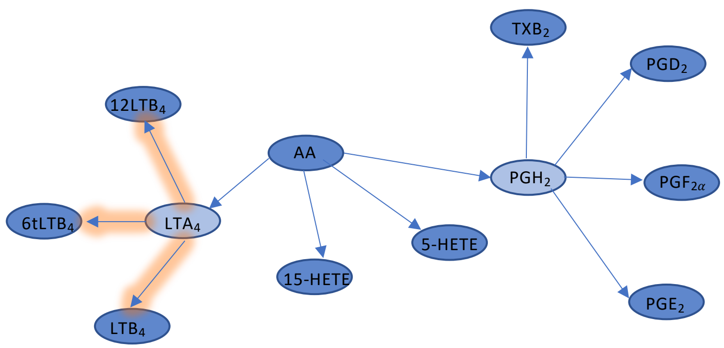

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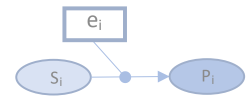
Reaction Framework: 

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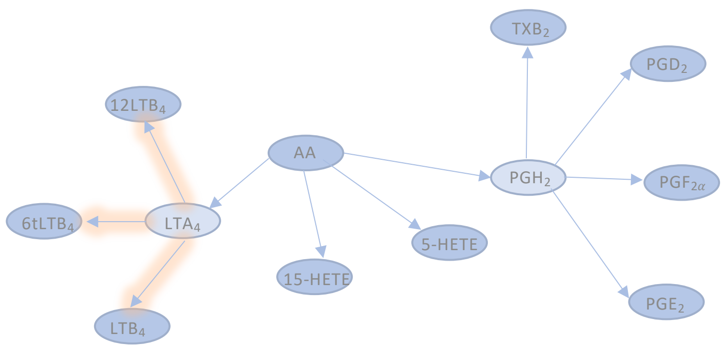


Enzyme Synthesis Control

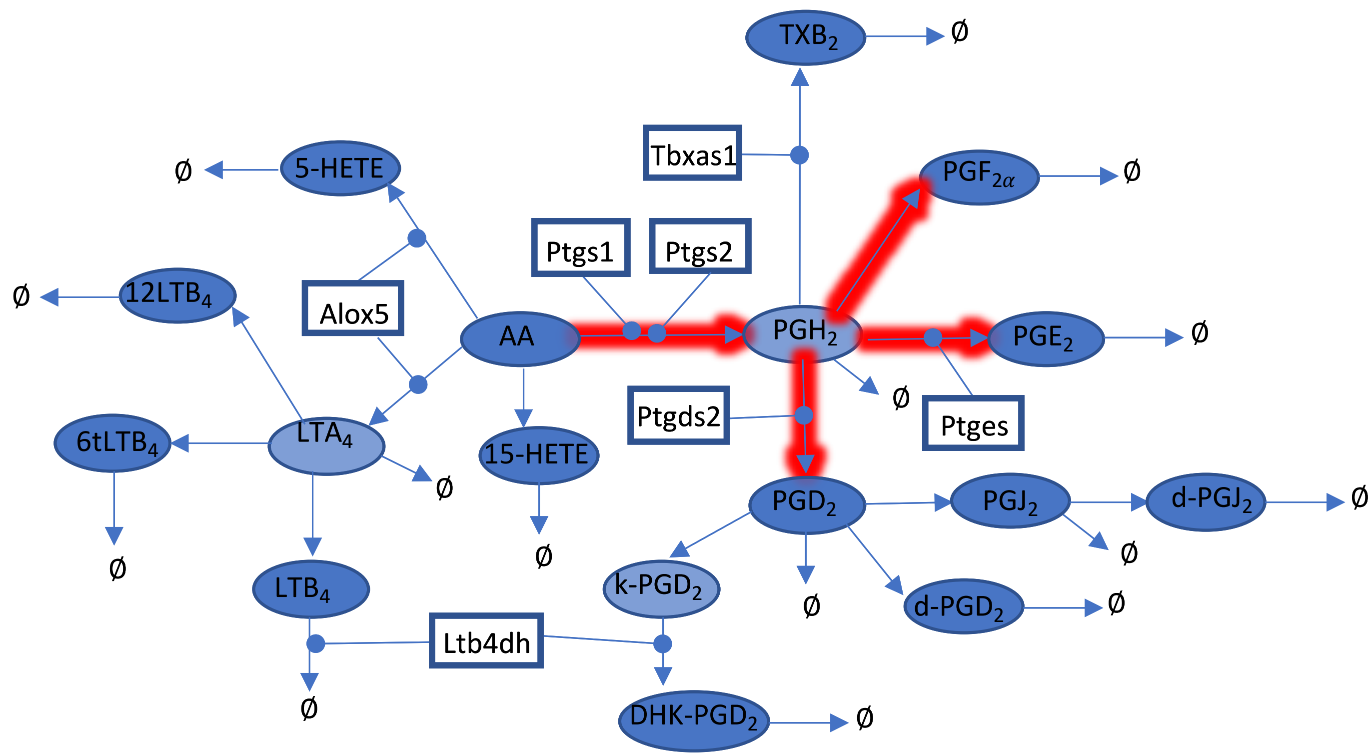
$$u_i = \frac{\rho_i}{\sum_j \rho_j}$$

Enzyme Activity Control

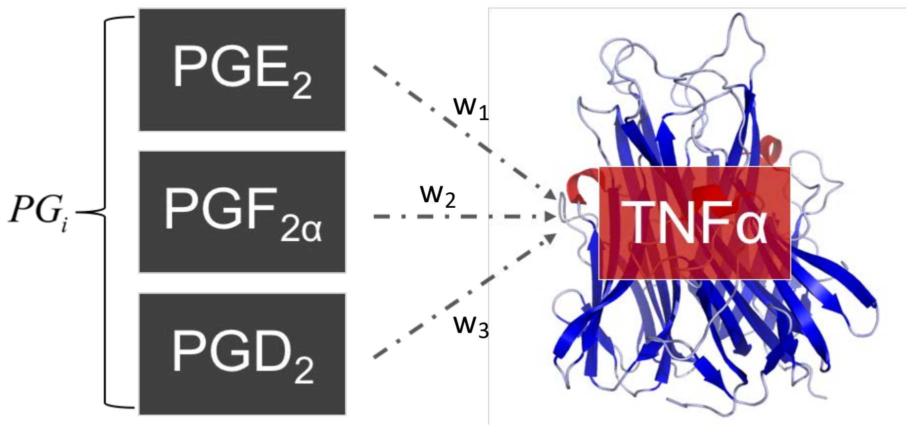
$$v_i = \frac{\rho_i}{max_j(\rho_j)}$$

What about the Cybernetic Goal
& How do we calculate $\rho_i = ?$

A closer look at Part 2



Defining the Cybernetic Goal



$$\text{TNF}\alpha = \sum_i w_i PG_i$$

The Cybernetic Variables

GOAL: "dynamically maximize TNFα"

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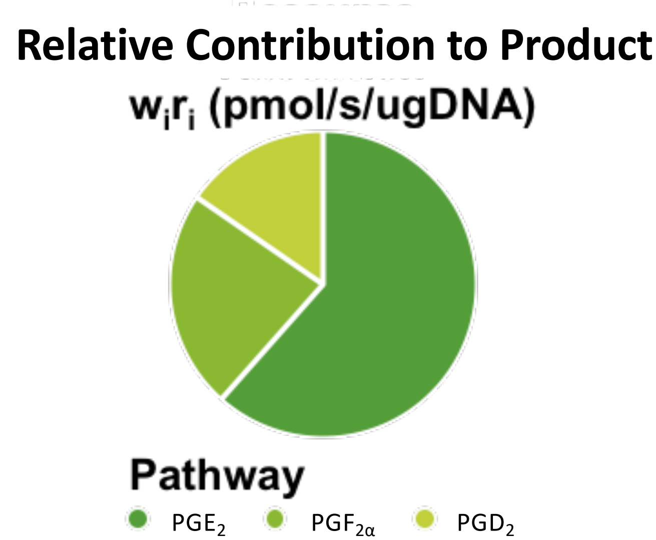

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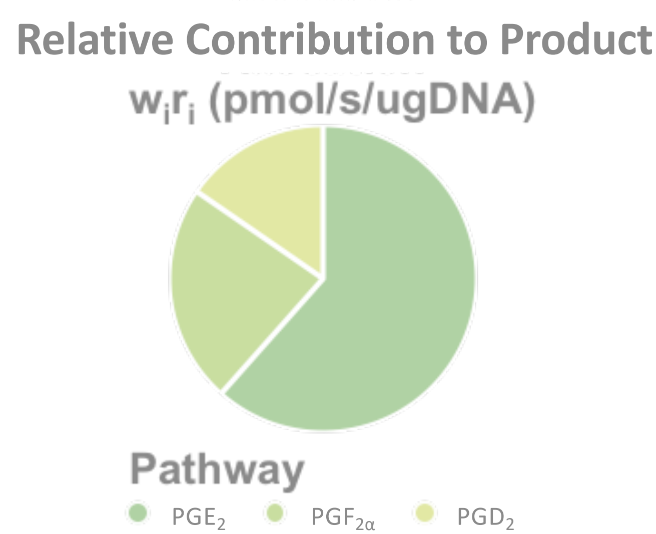
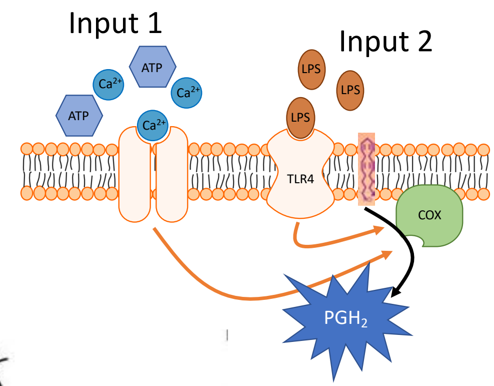
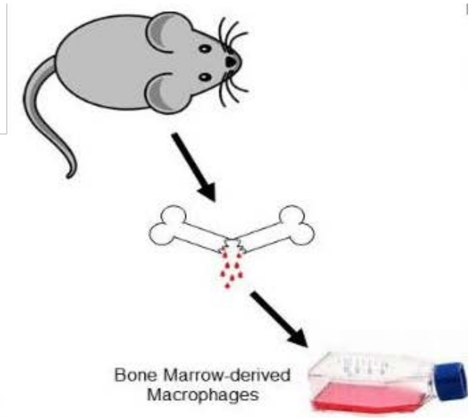


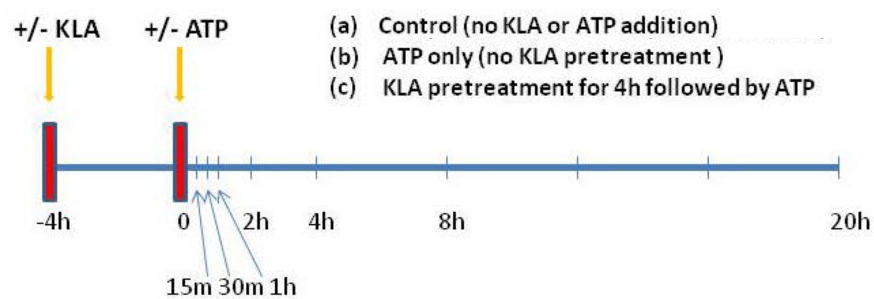
System Properties



Cell type:
Bone Marrow-Derived Macrophages

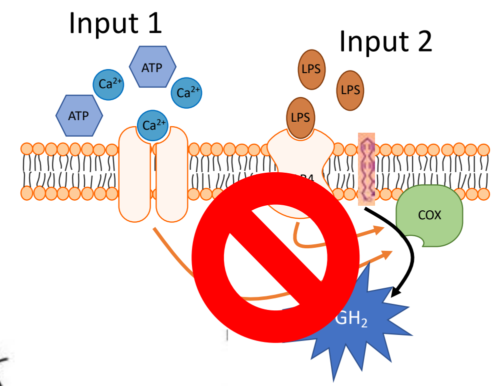


KLA/ATP timecourse on BMDM's: Experimental design



Lipid/mRNA measurements taken at 0 (ctrl only), 15m, 30m, 1h, 2h, 4h, 8h, 20h (relative to ATP addition)

System Properties



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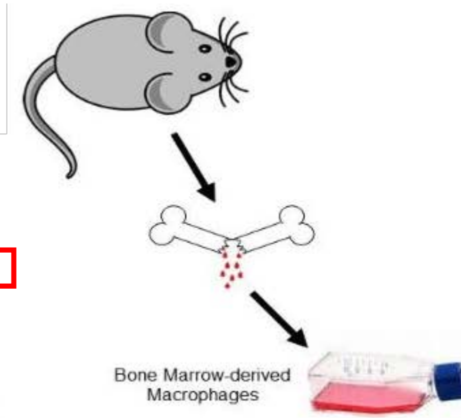

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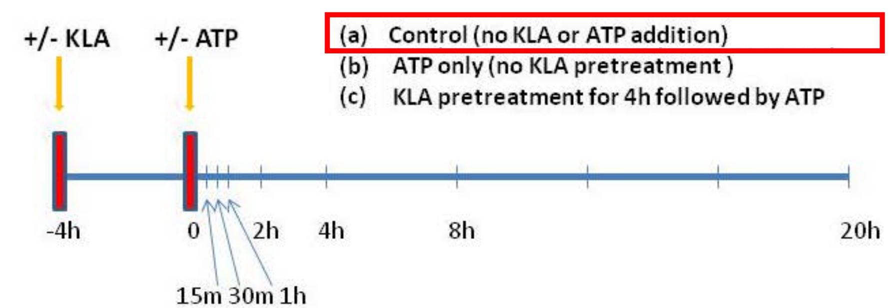

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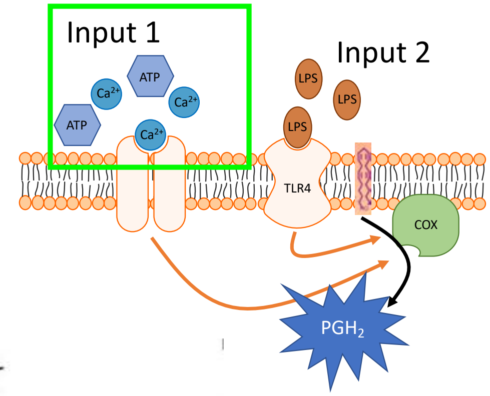

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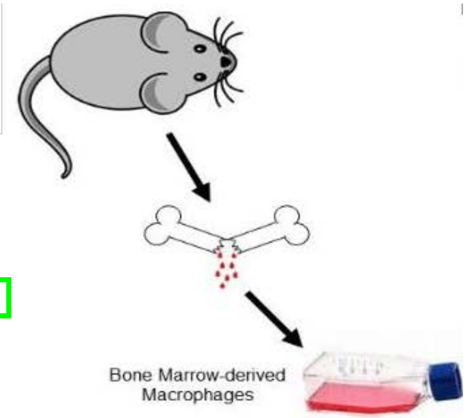

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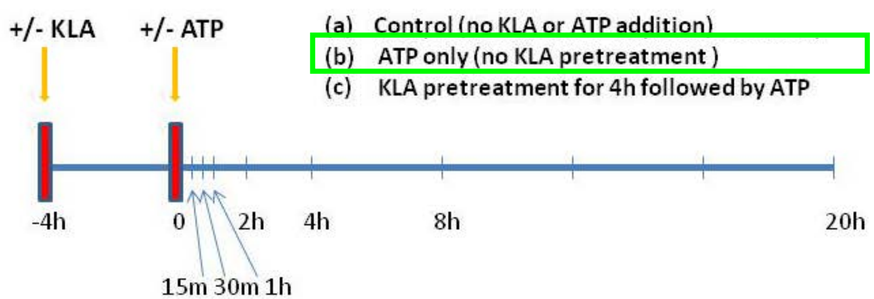

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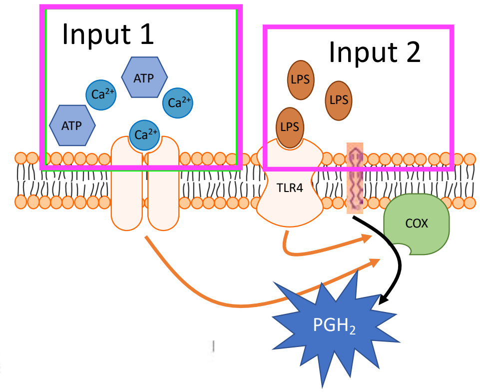

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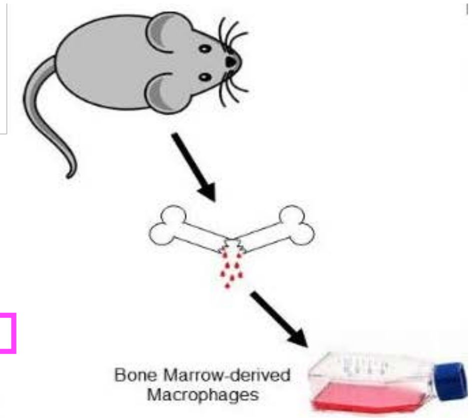
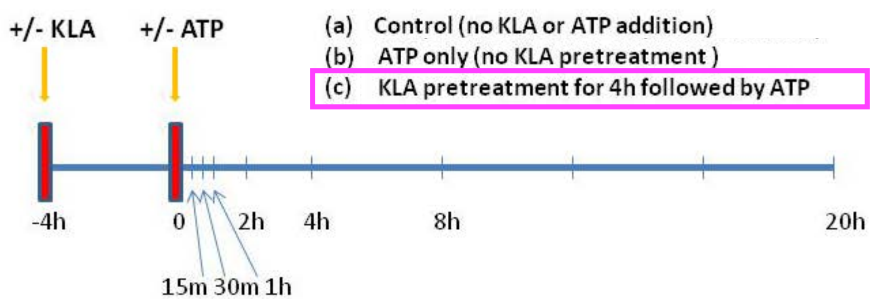


KLA/ATP timecourse on BMDM's: Experimental design



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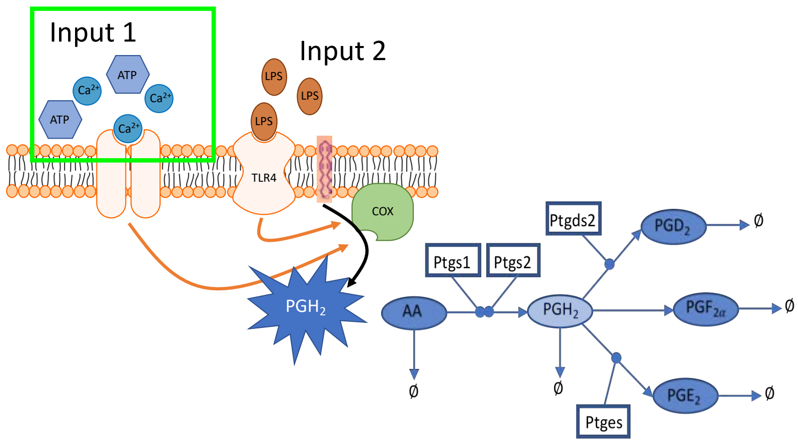
Parameter Estimation: Simulating ATP Stimulated BMDM Cells



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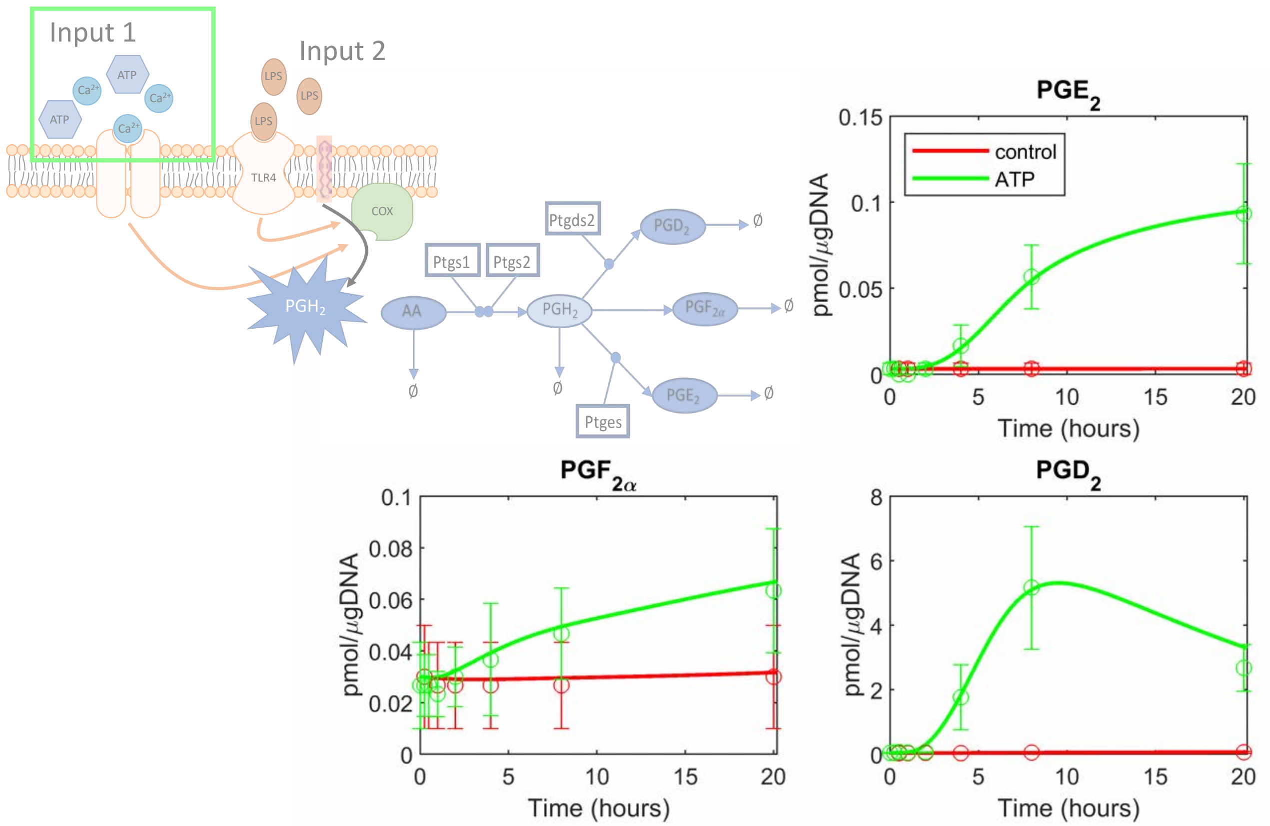
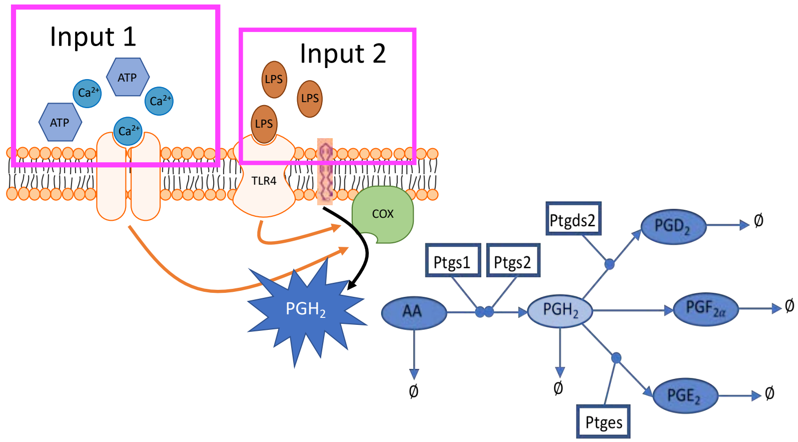
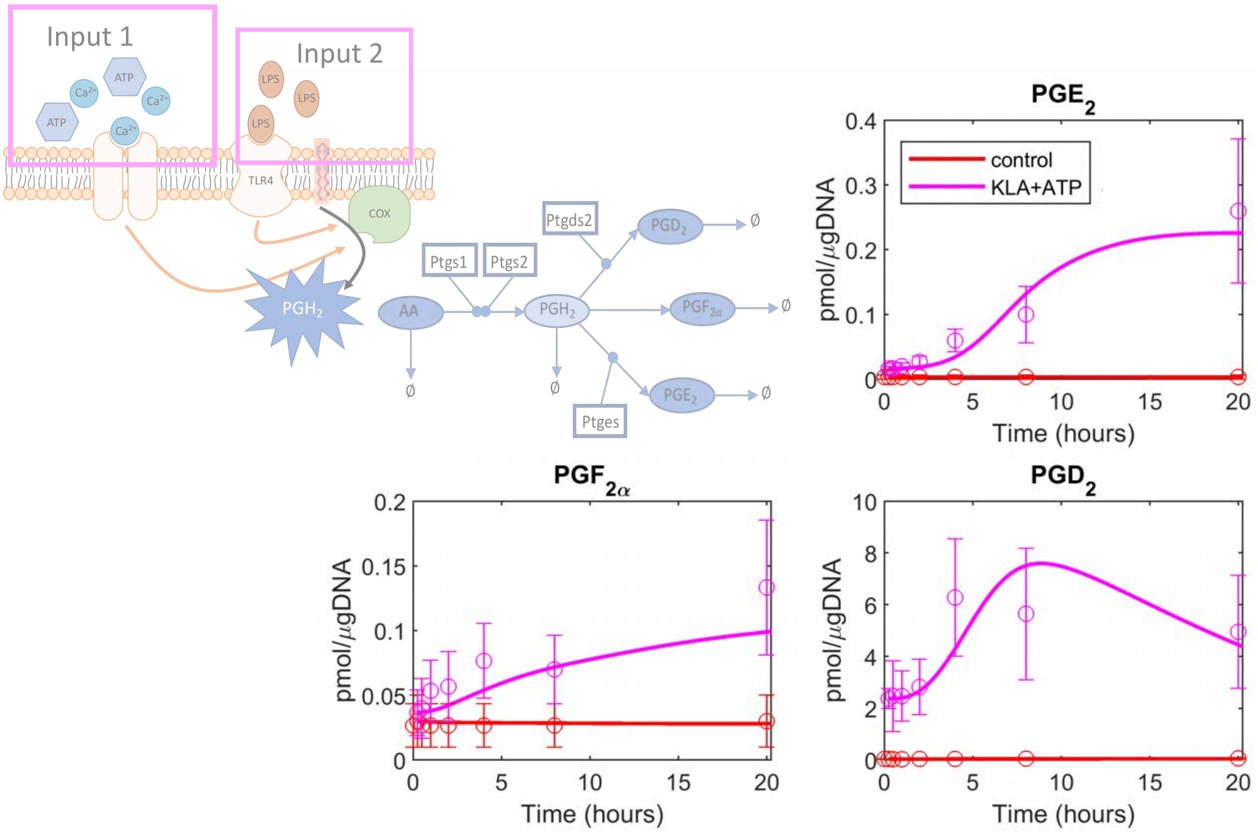


Model Validation: Predicting KLA Primed & ATP Stimulated BMDM Cells

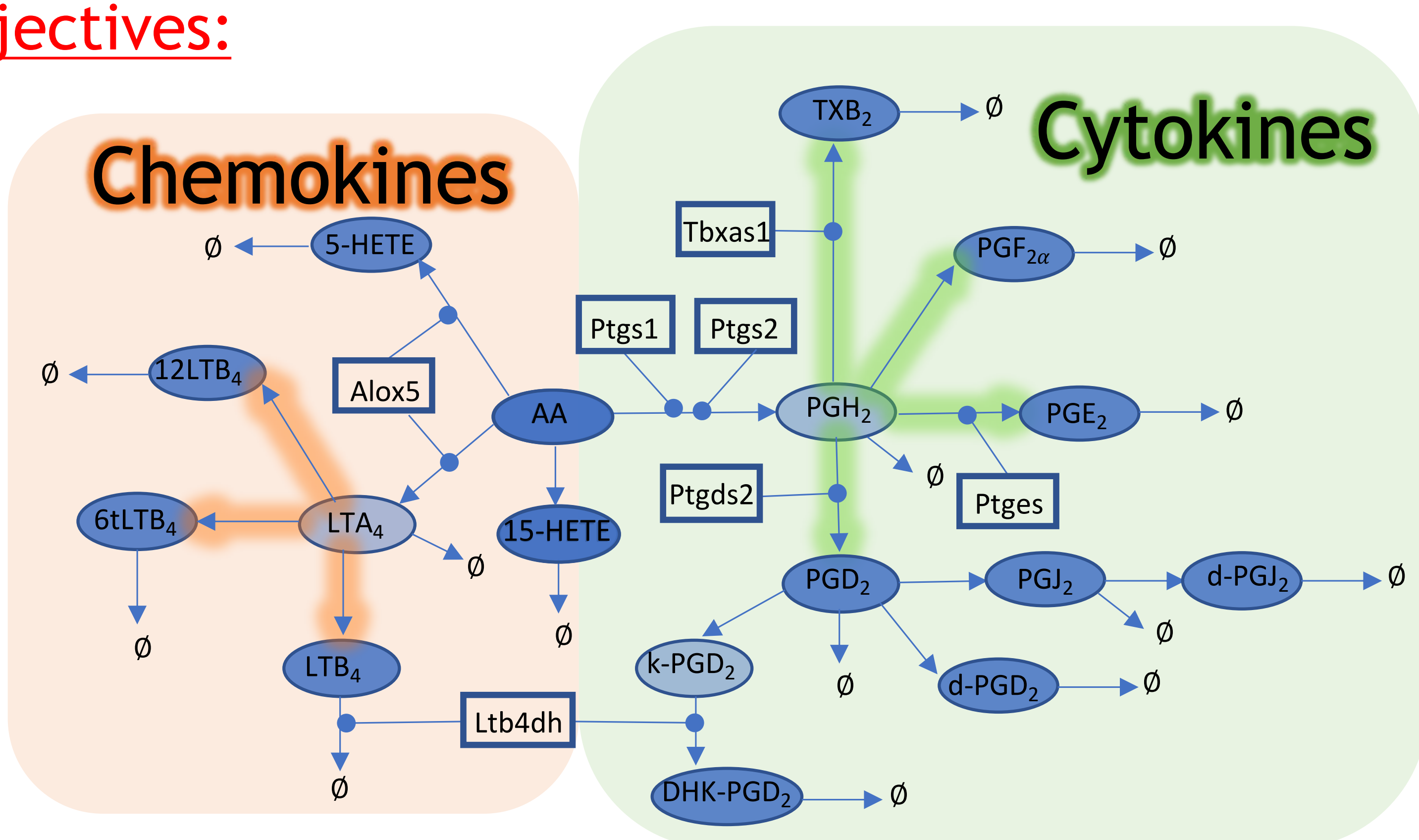


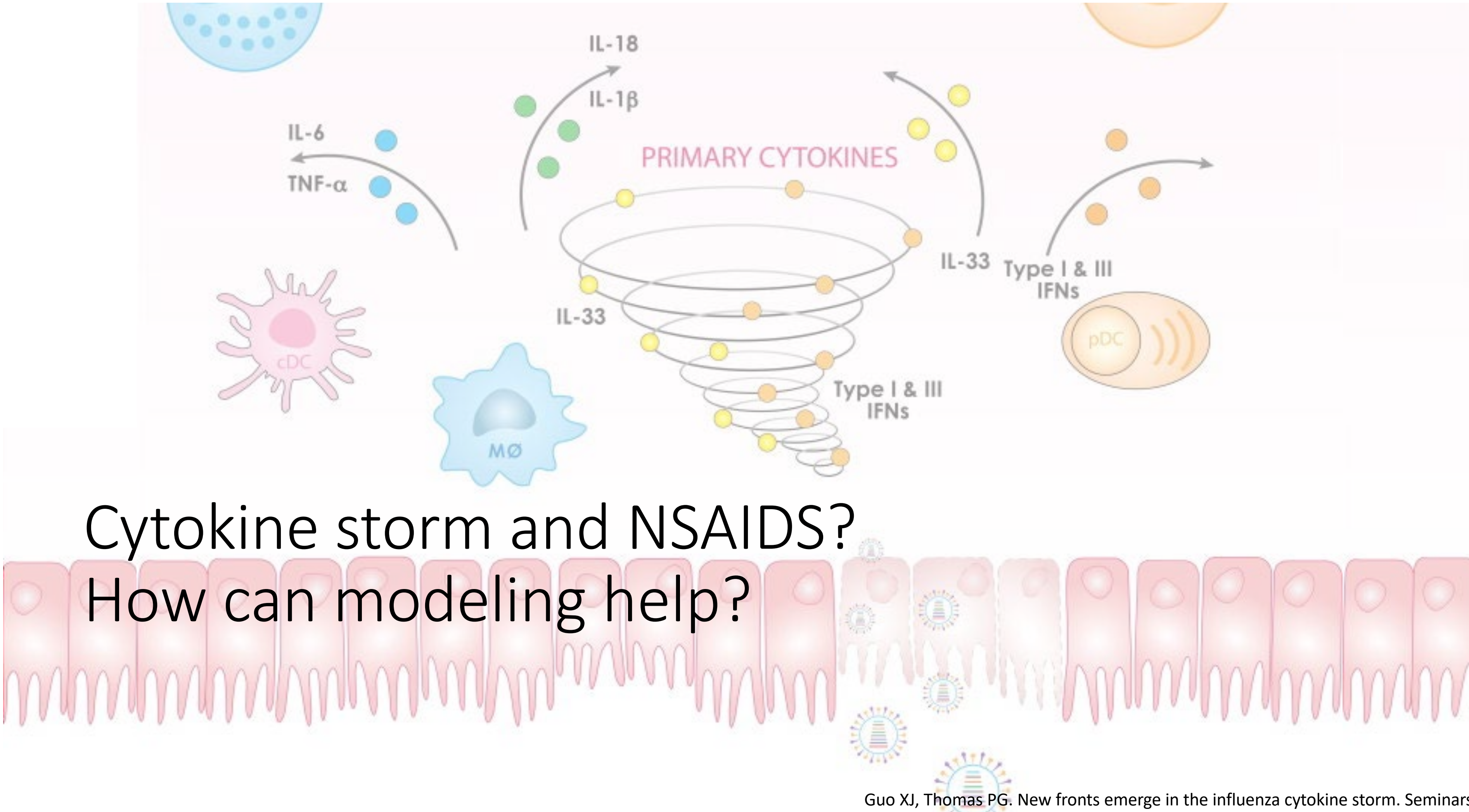
Model Validation: Predicting KLA Primed ATP Stimulated BMDM Cells



Cybernetic Model of Eicosanoid Metabolism

2 objectives:

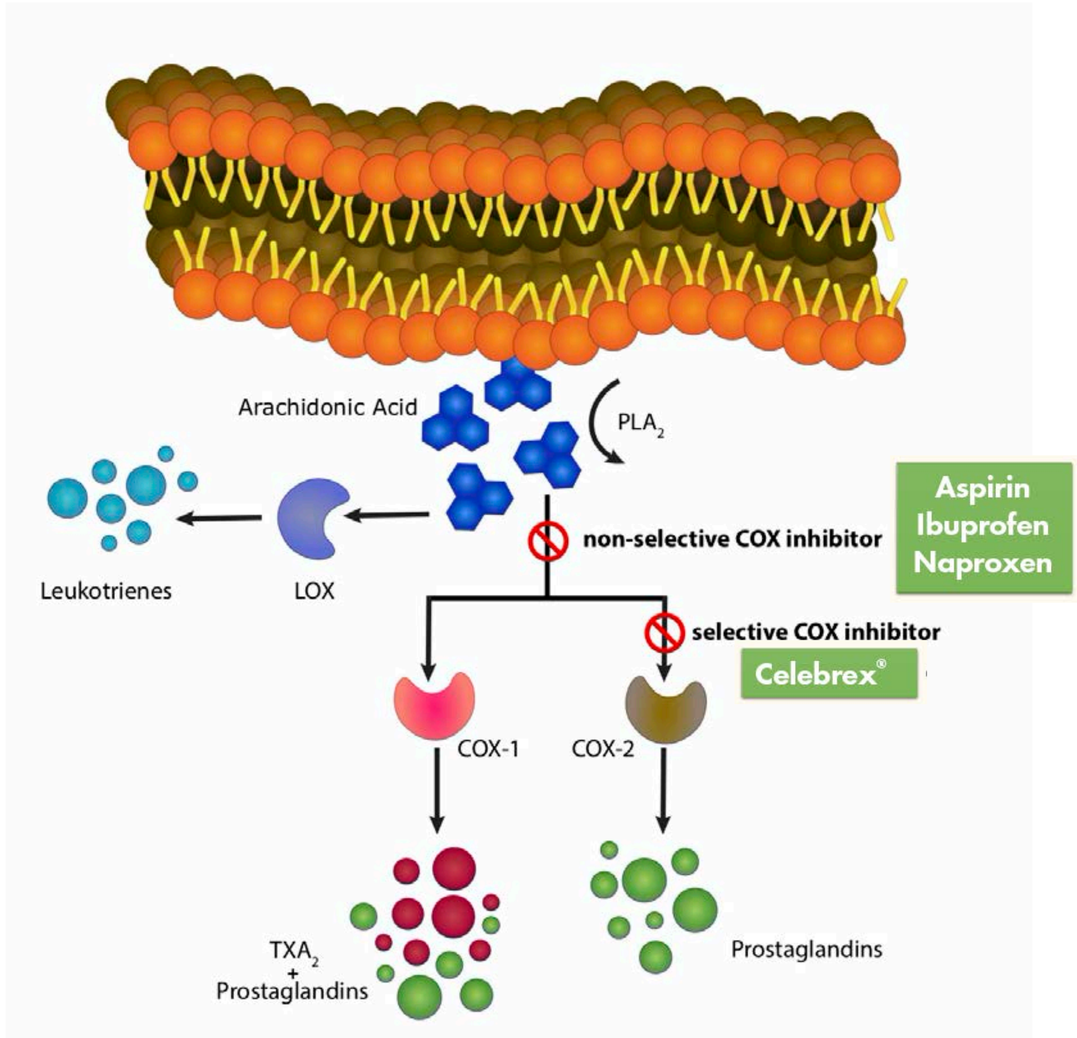




Cytokine storm and NSAIDS?
How can modeling help?

Guo XJ, Thomas PG. New fronts emerge in the influenza cytokine storm. Seminars Immunopathology. 2017 Jul;39(5):541-550. DOI: 10.1007/s00281-017-0636-y.

NSAIDs and COX



Special thanks to…

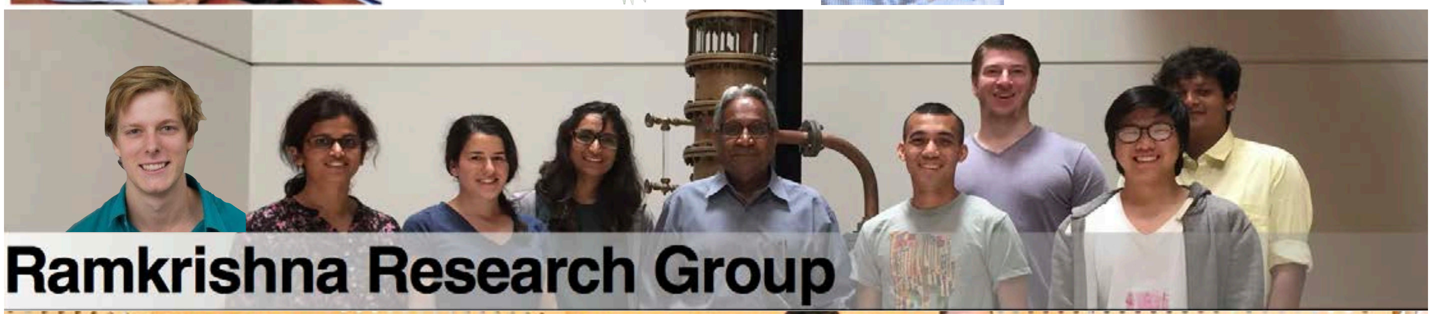
Center for
Science of Information
NSF Science and Technology Center

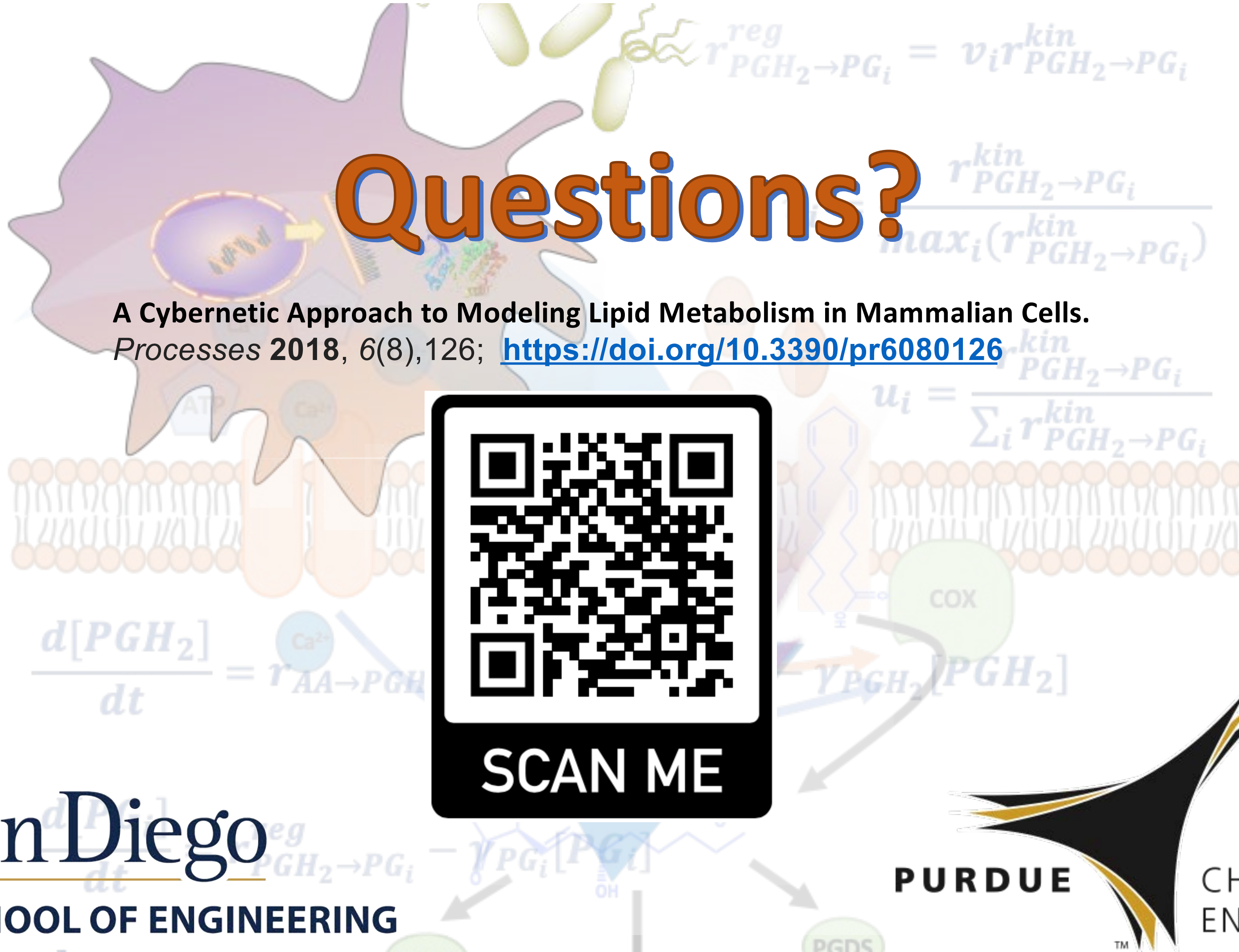
Dr. Doraiswami Ramkrishna
Harry Creighton Peffer
Distinguished Professor

PURDUE CHEMICAL ENGINEERING

Dr. Shankar Subramaniam
Distinguished Professor of
Bioengineering, Bioinformatics
and Systems Biology

UC San Diego
JACOBS SCHOOL OF ENGINEERING





Questions?

A Cybernetic Approach to Modeling Lipid Metabolism in Mammalian Cells.

Processes **2018**, *6*(8),126; https://doi.org/10.3390/pr6080126

SCAN ME

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